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Bridging genomics research between developed and developing countries: The Genomic Medicine Alliance

David N. Cooper¹, Angela Brand², Vita Dolzan³, Paolo Fortina⁴, Federico Innocenti⁵, Ming Ta Michael Lee⁶, Milan Macek Jr⁷, Fahd Al-Mulla⁸, Barbara Prainsack⁹, Alessio Squassina¹⁰, Effy Vayena¹¹, Athanassios Vozikis¹², Marc S. Williams¹³, George P. Patrinos^{14,*}

¹ Institute of Medical Genetics, School of Medicine, Cardiff University, Cardiff, United Kingdom; ² University of Maastricht, Institute of Public Health Genomics, Maastricht, the Netherlands; ³ University of Ljubljana, School of Medicine, Ljubljana, Slovenia; ⁴ Thomas Jefferson University, Kimmel Cancer Center, Philadelphia, PA, USA; ⁵ Institute of Pharmacogenomics and Individualized Therapy, University of North Carolina, Chapel Hill, NC, USA; ⁶ RIKEN Center for Genomic Medicine, Yokohama, Japan; ⁷ Charles University Prague and Faculty Hospital Motol, Institute of Biology and Medical Genetics, Prague, Czech Republic; ⁸ University of Kuwait, Molecular Pathology Unit, Safat, Kuwait; ⁹ King's College London, Department of Social Science, Health and Medicine London, United Kingdom; ¹⁰ University of Cagliari, School of Medicine, Department of Biomedical Sciences, Cagliari, Italy; ¹¹ University of Zurich, Institute of Biomedical Ethics, Zurich, Switzerland; ¹² University of Piraeus, Department of Economics, Piraeus, Greece; ¹³ Geisinger Health System, Genomic Medicine Institute, Danville, PA, USA; ¹⁴ University of Patras, School of Health Sciences, Department of Pharmacy, Patras, Greece

* Corresponding author at: University of Patras, School of Health Sciences, Department of Pharmacy, University Campus, Rion, GR-26504, Patras, Greece; Telephone/Fax: +30-2610969834, Email: gpatrinos@upatras.gr

Abstract

The Genomic Medicine Alliance [<http://www.genomicmedicinealliance.org>] is a newly created global academic research network that aims to establish and strengthen collaborative ties between academics, researchers, regulators and members of the public who are interested in genomic medicine. Its focus lies on the translation of scientific research findings into clinical practice. It brings together experts from disciplines including genome informatics, pharmacogenomics, public health genomics, ethics in genomics and health economics, and are supervised by a 14 member International Scientific Advisory Committee, comprising internationally renowned scientists. The Alliance's official journal, *Public Health Genomics*, offers members a highly respected publication forum for their original research findings. In the short to medium term, the Genomic Medicine Alliance hopes to broaden its membership significantly, and to initiate new projects not only to promote the translation of genomics research into clinical practice but also to harmonize research activities between developed and developing countries. It also seeks to support the mobility of early-stage researchers and scientists across borders, and the organization of educational activities in the field of Genomic Medicine.

Key words: Genomic Medicine, pharmacogenomics, Ethics in Genomics (genethics), whole genome sequencing, genome informatics, public health genomics, economic evaluation in genomic medicine, genome literacy, genetics education

Introduction

The central aim of genomic medicine is to utilize the individual's genomic information to support the clinical decision-making process [1]. In recent years, significant advances have been made in understanding the molecular etiology of a wide range of human genetic diseases. These advances have the potential to improve disease prognosis and treatment [2]. In parallel, genomic technology has progressed rapidly, prompting the replacement of low-throughput genetic screening methods by new high-throughput genome-wide screening and massively parallel sequencing approaches [3]. As a result, genomics research has the potential to aid clinicians in their task of estimating disease risk, as well as individualizing treatment modalities. This constitutes the basis of Genomic Medicine, a new specialty that promises to enhance opportunities for the customization of patient care including the personalization of conventional therapeutic interventions [4].

Although the concept of Genomic or Personalized Medicine is relatively new, its intellectual predecessors have been around for some considerable time. Thus, a Around 400 B.C.E., Hippocrates of Kos (460 ~~B.C.~~ 370 B.C.E.) stated that "... it is more important to know what kind of person suffers from a disease than to know the disease a person suffers". ~~Also~~ In addition, Ibn Sina (c.980-1037 C.E.) ~~stated~~ opined that "...in the make-up of most people there is somewhere a natural tendency to get out of order, some congenital weakness in one particular organ, tissue or system". Ibn Sina ~~called~~ termed this a "personal disposition" and put forward the view that each patient ~~is~~ should be looked upon as a distinct and separate case. The first application of "Genomic Medicine" is codified in the Talmud. The Talmud (Yevamot 64b) relates Rabbi Judah the Prince's ruling [2nd century B.C.E.] that if a woman's first two children had died from blood loss after circumcision, the third son should ~~not~~ be excused circumcised. Rabbi Simeon ben Gamliel disagreed and ruled that the third son might ~~ay~~ be circumcised, but if this infant also died then the fourth child should not be

circumcised. These ~~two~~ Rabbis did however agree~~d~~ that the abnormal bleeding tendency was hereditary, but disagreed as to how many repe~~a~~titive events were required to establish a pattern ~~and therefore~~justifying exemption of a child from circumcision. These ancient statements and examples together probably encapsulate the essence of modern personalized genomic medicine. At present, several international organizations and research consortia are harmonizing their efforts with ~~a view to~~the aim of supporting the translation of genomic research into clinical practice so that genomic medicine can ultimately be used to benefit the global community (Table 1).

The Genomic Medicine Alliance [GMA; 101] is a newly established global academic research network. It aims to build and strengthen collaborative ties between academics, researchers, regulators and those members of the general public who are interested in genomic medicine. The GMA focuses particularly on the translation of new research findings into clinical practice in developed, but most importantly, in developing countries.

Aims and goals of the Genomic Medicine Alliance

First and foremost, the GMA aims to: (a) Encourage and catalyze multidisciplinary collaborative research between partner institutions and scientists, particularly from developing countries, (b) Liaise between research organizations, clinical entities and regulatory agencies in areas related to genomic medicine, (c) Facilitate the introduction of pharmacogenomics and advanced omics technologies into mainstream clinical practice, (d) Propose guidelines and draw up recommendations in all areas pertaining to genomic medicine, in close collaboration with other scientific academic entities, agencies and regulatory bodies, and, (e) Develop independently and coordinate, in close collaboration with partner institutions, ~~and coordinate~~ educational activities in the area of genomic medicine.

The main goal of the GMA is to encourage stronger collaboration between genomics research in developed and developing/low resourced countries. Such a ~~stronger-strengthening~~ of collaboration is likely to create benefits for all parties. Developing countries will undoubtedly benefit from training opportunities, knowledge exchange, and ~~from~~ expanding transnational networks. Developed countries are likely to benefit through comparative work on families with rare diseases or unique clinical features ~~and rare diseases~~. Considering that approximately 85% of the world's population live in developing countries, this represents a major ~~potential opportunity, and to access a~~ hitherto largely untapped, source of information ~~on and biosamples from~~ people with rare disorders. Rare disorders, while important to understand for the affected patient and their families, have also provided key insights which ~~have led-leading~~ to breakthroughs in our understanding of gene function in disease and development. They have also played a crucial role in the identification of pathways that are essential to human health [110]. Further, a key requirement for the global success of GMA will be to prepare the path from genomics research to Genomic Medicine, by encouraging and undertaking multicenter research projects in key sub-disciplines. To this end, GMA activities aim to contribute ~~in-to~~ the transition from genomics and pharmacogenomics research to Genomic Medicine, viz. Public Health Genomics, Ethics in Genomics (or 'genethics'), Genome Informatics, the genetics education of healthcare professionals, genetics awareness of general public and health economic evaluation in relation to genomic medicine. Even if genomic and pharmacogenomics research ~~are-represent~~ the bedrock of genomic medicine, supporting pillars will still need to be erected for the superstructure to hold: The areas identified in **Figure 1** constitute these pillars. At present, although the foundations of genomic medicine are becoming stronger and ~~met-with~~ being attributed ever-increasing hopes and expectations, the pillars ~~upon-themselves~~ are still largely under construction.

GMA research activities are accompanied by an International Scientific Advisory Committee comprising 14 internationally renowned scientists in the field, from Asia (Ming Ta

Michael Lee) and the Middle East (Fahd Al-Mulla) to Europe (Angela Brand, David N. Cooper, Vita Dolzan, Milan Macek Jr, George P. Patrinos, Barbara Prainsack, Alessio Squassina, Effy Vayena, Athanassios Vozikis) and the USA (Paolo Fortina, Federico Innocenti, Marc S. Williams). Administrative assistance is provided by the Golden Helix Foundation [102] staff. Registration with the GMA is free-of-charge, to encourage the participation of researchers from developing and low-income countries. Upon registration, members specify their research interests so that they can be directed to research projects and training opportunities that suit their needs.

GMA research activities span six different Working Groups, namely Genome Informatics, Pharmacogenomics, Cancer Genomics, Public Health Genomics, Genethics and Economic Evaluation in Genomic Medicine. Each of the Working Groups' activities are coordinated by the corresponding Working Group and Activity leaders in conjunction with Senior National Representatives from each of the >50 countries from which the >250 current GMA members (April 2014) originate (**Fig. 2**). Below, we summarize some of the key GMA research projects.

Current research projects among GMA members

Genome Informatics Working Group

Documentation of the incidence of genetic disorders in different populations, particularly in those developing countries with a high incidence of genetic diseases and/or consanguinity can be particularly helpful in the context of adopting national prevention and screening programs [5]. GMA members currently participate in the development of three new National/Ethnic Genetic databases for the Kuwaiti, Moroccan and Bahraini populations to document the incidence of genetic disorders in these countries. In addition, five preexisting National/Ethnic Genetic databases for the Lebanese, Serbian, Cypriot, Greek and Egyptian

populations are currently being migrated to the new ETHNOS software [6], which has recently been upgraded to include new data querying and visualization functionalities [7]. The long-term goal is to expand this concept such that the ETHNOS software supports the development of several National Genetic databases [111], based on the data warehouse principle and pre-existing guidelines [8] that will be assigned to senior human geneticists in the corresponding populations in order to coordinate their curation and further data [5].

Members of the GMA have also helped to develop an electronic tool to translate pharmacogenomics research results into a format that is meaningful for clinicians [9]. Such a project is proceeding in close collaboration with other major European research initiatives, such as RD-Connect [112] in order to harmonize and develop common standards for databases and patient registries for rare diseases, and most importantly to develop clinical bioinformatics solutions, including data mining and knowledge discovery tools for the analysis and integration of molecular and clinical data to promote the discovery of new disease genes, pathways and therapeutic druggable targets.

Pharmacogenomics Working Group

Pharmacogenomics holds out the promise of rationalizing drug treatment by ~~by~~ optimizing the balance between treatment efficacy and toxicity based upon a comprehensive understanding of the impact of genomic variants combined with other patient-based and environmental factors. The Pharmacogenomics Working Group, in close collaboration with the Golden Helix Foundation, is currently taking part in the Euro-PGx project [113], in which 26 European populations are participating. More specifically, the Euro-PGx project aims to (a) determine the incidence [GEORGE: population frequencies?] of pharmacogenomics biomarkers to optimise medication modalities and to minimize adverse reactions by genotyping, in conjunction with the Pharmacogenomics for Every Nation Initiative [PGENI; 114], 1,936 pharmacogenomically-relevant genetic variants in 231 absorption, distribution,

metabolism, and excretion–toxicity (ADMET)-related pharmacogenes, which would assist in prioritizing medication selection in participating developing countries and, (b) develop off-the-shelf solutions for pharmacogenomic testing in participating developing countries. Preliminary findings suggest that European populations display functionally significant differences in terms of >130 pharmacogenomic biomarkers; the replication of these findings in larger population samples would establish a common framework for pharmacogenomic testing in developing countries.

The Pharmacogenomics Working Group has sought to provide ~~proof-of-~~principle of the use of whole-genome sequencing for pharmacogenomic testing, by resequencing with high coverage almost 500 whole genomes, mostly from Caucasian populations. This project not only revealed a vast number of novel potentially functional variants in a total of 231 pharmacogenes, as indicated by *in silico* analysis, but also demonstrated the value of whole-genome sequencing for pharmacogenomic testing by capturing over 18,000 variants in these pharmacogenes; this compares with just 250 variants that would have been identified in these genes using the most comprehensive pharmacogenomics screening assay currently available [10].

Public Health Genomics Working Group

Public Health Genomics represents the responsible and effective translation of genome-based knowledge and technologies into public policy and health services for the benefit of population health [11]. To this end, the Public Health Genomics Working Group is undertaking nationwide studies to better understand the level of the general public's genetics awareness including their attitudes to genomic testing and the level of healthcare professionals' (i.e. physicians, pharmacists, nutritionists, *etc*) genetics education. So far, such surveys have yielded some very interesting findings [12, 13] highlighting the relative lack of healthcare professionals' genetics education and general public's genetics awareness as

perhaps one of the biggest obstacles to the widespread implementation of Genomic Medicine [14,15]. They have also shown the ~~plural-general~~ utility~~ies~~ of genomic testing for individuals including the public's remarkable level of interest in participating in genomic research ~~participation~~ [16,17]. Such surveys are currently being replicated in other European countries to confirm these findings. To this end, GMA members co-organize educational events revolving around pharmacogenomics and Genomic Medicine in various European countries; these are endorsed by the GMA and partly funded by the Golden Helix Foundation and other entities [18].

The Public Health Genomics Working Group has engaged with a stakeholder analysis to determine the measures to be undertaken to expedite the genomic information-based medical decision-making process.

Genethics Working Group

Several ethical issues confront those of us who are committed to the practice of Genomic Medicine, including the regulation of genetic testing, the governance of genetic research, and genomic data sharing in an ethical and publicly accountable way [19]. The GMA Genethics Working group also explores the landscape of direct-to-consumer (DTC), beyond-the-clinic (BTC) [20] and over-the-counter (OTC) genetic tests in various European countries, including Greece [12], Slovenia, Italy and Serbia. It is particularly important to harmonize policies that safeguard the general public and ensure that they ~~are~~ become better informed with respect to the various attendant risks from this type of testing. Currently, regulation ~~of~~ these issues is lacking in many European countries, as well as at a central level in the form of a directive of the European Medicines Agency for both OTC and DTC genetic testing [21]. The GMA has recently produced an opinion article to highlight the various types of OTC genetic tests currently available [22]. GMA members are also working together with

the National Genetic Societies and National Ethics Committees to establish guidelines to cover ethical, legal and social issues pertaining to genetic testing.

Economic Evaluation in Genomic Medicine Working Group

A key factor in expediting the adoption of Genomic Medicine in clinical practice would be the demonstration of its cost-effectiveness (as the “fourth hurdle” in health-care, after safety, efficacy and quality). The real cost effectiveness of involving genomics in medicine is unknown ~~excepting certain~~apart from some rather limited studies in pharmacogenomics and hereditary cancer syndromes. Realizing its effectiveness would be a crucial step towards convincing policy makers of the utility of genomics in healthcare as a means to reduce the cost of treatments, as well as the overall burden and consequences of diseases at the national level [23,24]. Currently, GMA members are involved in cost-effectiveness and cost-utility analyses of warfarin (Croatia), acenocoumarol (Serbia and Greece) and clopidogrel (Serbia) anticoagulation treatments, and preliminary findings suggest that warfarin treatment is indeed cost-effective in Croatia [Mitropoulou C, Fragoulakis V, and co-workers, in preparation]. Future work is already in progress and includes drugs for cancer and hematologic malignancies treatment, while it is envisaged~~ioned~~ that the workgroup will eventually develop and evaluate standardized methodologies for economic evaluation of genomic medicine [25], which will be of utmost importance in such a rapidly evolving discipline.

The GMA has recently endorsed the production of the textbook “Economic Evaluation in Genomic Medicine” that is co-authored by two GMA Scientific Advisory Committee members and will be published by Elsevier/Academic Press in early 2015.

Future perspectives: A roadmap of GMA activities

The GMA is a new initiative in the field of Genomic Medicine with the primary goal of encouraging the participation of developing and low-resourced ~~countries~~settings. In contrast to other Genomic Medicine initiatives and consortia (**Table 1**), the GMA has several unique features as a research consortium, namely free membership, a flat governance structure and above all, a commitment to bring together genomics research institutions from developing countries with those from developed countries. The official inaugural meeting of the GMA will be the forthcoming 2014 Golden Helix Symposium in Belgrade, Serbia (30 October - 2 November 2014).

The rapid expansion of the GMA membership base~~is~~ is a top priority of the International Scientific Advisory Committee. The focus will be placed primarily on developing countries in the Middle East, Asia and Latin America. Another route to expanding the membership base will be official partnerships with other Genomic Medicine consortia and international collaborative efforts. To this end, there is already a memorandum of understanding in place between the GMA and the SEAPharm consortium to pursue common goals particularly in the field of Pharmacogenomics, while GMA Scientific Advisory Committee members participated in the National Human Genome Research Institute-supported Global Leaders in Genomic Medicine meeting in Washington DC, USA [January 8-9, 2014; 116]

An important milestone for GMA was the recent agreement with Karger to establish the international peer-reviewed journal *Public Health Genomics* [115] as the Official GMA journal. *Public Health Genomics* is the leading bimonthly international journal focusing on the translation of genome-based knowledge and technologies into public health, health policies and healthcare as a whole. This partnership not only provides GMA members with a highly respected ~~publication~~ forum ~~for to publish~~ their original research findings but also with discounts on journals and books.

Regarding the various ongoing GMA research activities, the focus will be firmly placed on those projects that will deliver tangible results in relation to the translation of genomics research into clinical practice, e.g., the elucidation of the molecular basis of rare disorders, bioinformatics solutions to translating genomic results into clinically meaningful formats and accommodating whole genome sequencing data storage in an aggregate manner. Another strong focal point for the next two years will be projects in the field of health economic evaluation in genomic medicine to study the cost-effectiveness of pharmacogenomic testing. In addition, and in order to support the transnational mobility of students and junior researchers, the GMA plans to launch short- and long-term research fellowships for early-stage researchers from developing countries to pursue research in Centers of Excellence in developed countries. The GMA envisages doing this in collaboration with the Golden Helix Foundation and other charities.

Last but not least, the GMA will continue to endorse conferences and educational activities in the field of Genomic Medicine in Europe, the Middle East, Latin America and Southeast Asia. In addition, in conjunction with the Golden Helix Foundation [102], it has already established the Golden Helix Summer Schools [116]. This international initiative in the field of Genomic Medicine and Genome informatics aims to provide researchers around the world with the opportunity to expand their knowledge in the rapidly evolving field of Genomic Medicine and to exchange innovative ideas in the most conducive environment of the Greek islands.

In essence, the GMA aspires to become a focal point for harmonizing research activities in the field of genomic medicine between developed and developing countries and while further cultivate helping to pave the way for a smoother transition from genomics research in to genomic medicine.

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103. European Alliance for Personalized Medicine – <http://euapm.eu>
104. PerMed Coordination & Support Action (CSA)- <http://www.permed2020.eu>
105. European Personalized Medicine Association (EPEMED) – <http://www.epemed.org>
106. European Society of Predictive Medicine (EUSPM) – <http://www.euspm.org>
107. Personalized Medicine Coalition (PMC) - <http://www.personalizedmedicinecoalition.org>
108. South East Asian Pharmacogenomics Consortium (SEAPharm) -
<http://seapharm.pharmagtc.net/index.php/index.php>
109. Global Alliance for Genomics and Health – <http://www.ga4gh.org>
110. NIH Medline Plus: The Promise and Payoff of Rare Diseases Research, From NIH
Director Dr. Francis S. Collins –
<http://www.nlm.nih.gov/medlineplus/magazine/issues/spring11/articles/spring11pg2-3.html>
111. ETHNOS Databases – <http://www.findbase.org/index.php/ethnos-databases>
112. RD-Connect – <http://www.rd-connect.eu>
113. Euro-PGx project – <http://www.goldenhelix.org/index.php/research/pharmacogenomics-in-europe>
114. Pharmacogenomics for Every Nation Initiative (PGENI) – <http://www.pgeni.org>
115. Public Health Genomics - <http://www.karger.com/Journal/Home/224224>

Field Code Changed

116. The Golden Helix Summer Schools – <http://summerschools.goldenhelix.org>

117. Global Leaders in Genomic Medicine – <https://www.genome.gov/27555775>

Figure 1.

Graphical depiction of the GMA research activities that aim to translate Genomics Research and Pharmacogenomics into Genomic Medicine (see also text for details).

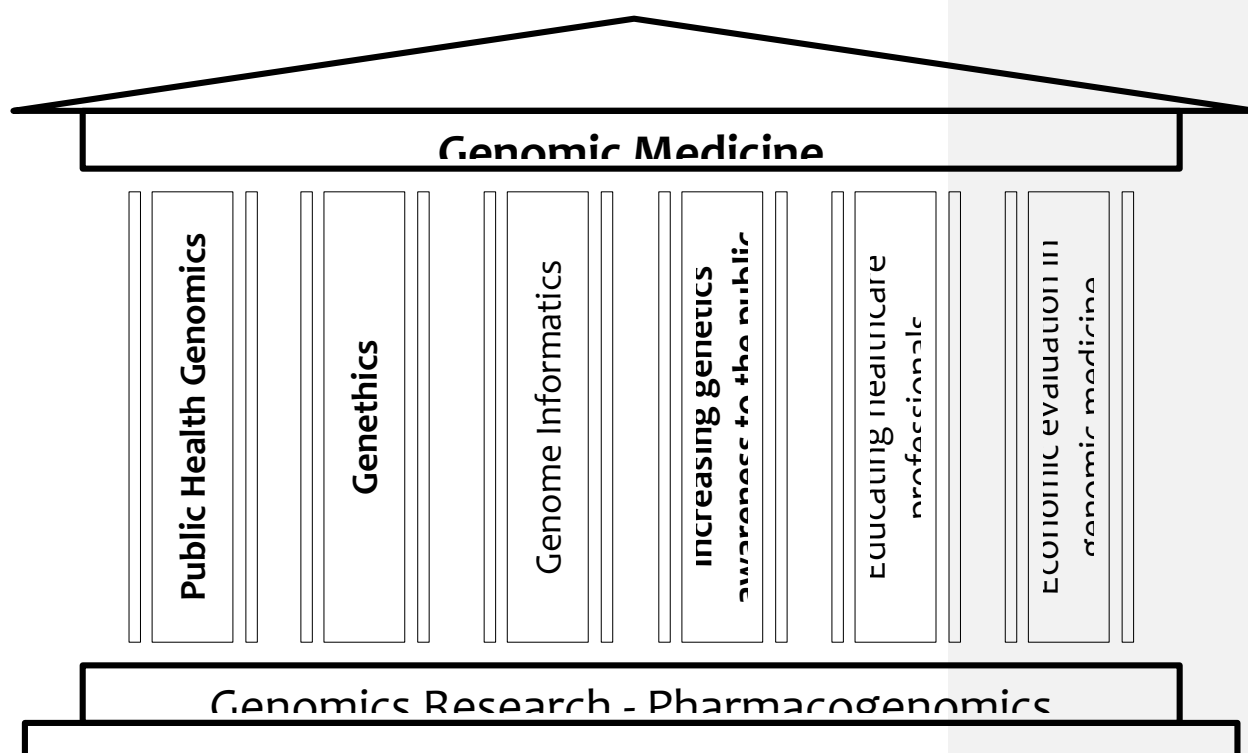


Figure 2.

Outline of GMA membership status. The GMA is coordinated by a 14-member Scientific Advisory Committee, assisted by the Working Group leaders and Senior National Representatives from more than 50 countries, from which the GMA members originate.



Table 1. Summary of the major international organizations involved in the field of Personalized Medicine. N/A: Not yet available

Organization	Type	Activities description	Region	Website
European Alliance for Personalized Medicine (EAPM)	Policy - advocacy group	EUAPM aims to position personalized medicine within the broader context of personalized healthcare, promote the understanding of personalized healthcare by patients, professionals and policy makers, catalyze the shaping not only of EU policy discussions, introduce incentives for personalized healthcare and create a favorable reimbursement environment for personalized medicines & companion diagnostics.	Europe	103
PerMed	European project	PerMed aims to complement existing activities by identifying and promoting promising research topics, developing strategic research and innovation agendas in Europe and beyond, and to bringing forward the implementation of Personalized Medicine for the benefit of society at large.	Europe	104
European Personalized Medicine Association (EPEMED)	Non-profit Organization	EPEMED aims to make personalized medicine a practical reality in Europe by focusing on the patient's access to innovations in this area, particularly for-with <u>respect to</u> co-dependent drug-companion diagnostics technologies.	Europe	105
European Society for Predictive Medicine (EUSPM)	Scientific Society	EUSPM aims to promote predictive medicine among healthcare professionals and to engage in educational activities to promote the concept of predictive	Europe	106

		medicine.		
Personalized Medicine Coalition (PMC)	Policy - advocacy group	PMC represents a broad spectrum of more than 225 innovator, academic, industry, patient, provider and customer communities. It aims to educate both the general public and policymakers by promoting new ways of thinking about health care and by advancing the understanding and adoption of personalized medicine and its products for the benefit of patients.	United States	107
South East Asian Pharmacogenomics Research Network (SEAPHARM)	Research Consortium	SEAPHARM aims to strengthen mutual cooperation and facilitate sustainable and equitable growth of the Pharmacogenomics community, and to promote further cooperation and linkage through seminars, exhibitions, workshops, technical assistance, scholarship schemes, training, and joint R&D projects, and where possible to exchange information, experience, know-how, technology and best practices, in the field of Pharmacogenomics.	Southeast Asia	108
Global Alliance for Global Health (GA4GH)	Research Consortium	GA4GH aims to accelerate progress in human health by helping to establish a common framework of harmonized approaches to enable effective and responsible sharing of genomic and clinical data, and by catalyzing data-sharing projects that drive data sharing and demonstrate its value.	International	109
Global Genomic Medicine Consortium (G2MC)	Research Consortium	G2MC aims to develop into a global effort to serve the goals of personalized medicine	International	N/A